IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of: Rima Kadurrah-Daouk *et al.*	Group Art Unit: 1634
Serial No.: 10/695,265	
Filed: October 27, 2003	Examiner: Heather Calamita
For: METHODS FOR DRUG DISCOVERY, DISEASE TREATMENT, AND DIAGNOSIS USING METABOLOMICS	
Attorney Docket No.: MBZ-001CP	

MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF JOHN RYALS UNDER 37 CFR §1.132

Dear Sir:

I, John Ryals, a citizen of the United States, residing in Cary, North Carolina, hereby declare as follows:

1. I am presently the Chief Executive Officer of Metabolon, Inc. (Durham, North Carolina). I have been working in the area of metabolomics for approximately 8 years. A copy of my curriculum vitae is attached as Appendix A.

2. I have read the above-referenced application (included herewith as Appendix B) and presently pending claims 91, 95, 96, and 140-149 (included herewith as Appendix C). It is my understanding that the invention is directed, at least in part, to a method for metabolomically identifying compounds indicative of a neurological disorder in a subject. The methods include the steps of obtaining a small molecule profile from a subject suspected of having and/or having a disease state; and comparing the small molecule profile from the subject to a standard small molecule profile.

4. In addition, I understand that claims 91, 95, and 96 have been rejected by the Examiner as lacking enablement under 35 U.S.C. § 112, first paragraph. The Examiner alleges that the specification does not reasonably provide enablement for determining the presence of or predisposition for any disease based on a small molecule profile and that it does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

5. The claimed invention is supported by the disclosure in the specification, in such a way as to enable one of ordinary skill in the art at the time the application was filed to practice the invention. The following examples show how an ordinarily skilled artisan, at the time the application was filed, would have been able to use the methods described in the specification to identify small molecules indicative of particular nervous system disorders.

In the following examples, samples were taken from both subjects with specific nervous system disorders and control subjects. The subjects were both male and female and varied in age. Samples of plasma were obtained from the subjects and analyzed using techniques such as GC-MS and LC-MS. Individual compounds were further identified using techniques known in the art, such as NMR. These techniques were described in the specification, as originally filed, for example, at least at page 13, lines 12-16 and page 71, lines 6-11.

Once obtained, the concentrations of particular small molecules for each disorder were graphed using computer programs. Generally, the data was organized such that the zero point on the X-axis was the mean for the control group (e.g., the standard small molecule profile). Each data point was expressed as the number of standard deviation units from the zero point. The Y-axis represents individual small molecules, with all points for a particular compound on the same horizontal line. Computer analysis of the data was described in the specification, as originally filed, for example, at least at page 7, line 30 through page 8, line 4.

Amyotrophic Lateral Sclerosis

For amyotrophic lateral sclerosis (ALS), plasma samples from healthy controls were compared to those of subjects suffering from ALS. The groups were matched with respect to age and gender.

When the small molecule profiles of the ALS subjects were compared to the healthy controls, it was found that the levels of four particular small molecules were

particularly indicative of ALS. These four molecules are xanthine, arachidonic acid, glutamic acid, and N-6-trimethyl lysine. By identifying subjects with concentrations of less than 1.5 N-6-trimethyl lysine, greater than 0.8 arachidonic acid, and greater than 0.77 xanthine, 97% of the subjects with ALS were identified with 77% specificity. The ability of the methods of the invention to distinguish between nervous system disorders is shown graphically in Figure 1, which compares small molecule profiles of subjects suffering from ALS to subjects suffering from peripheral neuropathy.

Alzheimer's Disease

For Alzheimer's disease, sixty control subjects and sixty subjects suffering from Alzheimer's disease were compared to each other and to thirty three subjects suffering from Mild Cognitive Impairment (MCI) and twenty seven MCI subjects who were progressing to Alzheimer's disease. The groups were matched with respect to age and gender.

Figures 2-5 compare the average concentration of particular small molecules for subjects suffering from Alzheimer's disease compared with subjects suffering from MCI, subjects suffering from MCI progressing to Alzheimer's disease and control subjects. The figures show that there is a clear difference between the controls and subjects suffering from MCI, Alzheimer's and subjects progressing from MCI to Alzheimer's disease.

Huntington's Disease

For Huntington's disease, plasma samples from sixteen healthy controls were compared to those of forty five subjects suffering from Huntington's disease. The groups were matched with respect to age and gender.

In Figure 6A and 6B, the small molecule profile of the controls were compared to that of the subjects having Huntington's disease. The subjects suffering from Huntington's disease showed much more variation in the concentrations of many different metabolites.

Parkinson's Disease

For Parkinson's disease, plasma samples from sixty healthy controls were compared to those of sixty subjects suffering from Parkinson's disease. The groups were matched with respect to age and gender.

In Figure 7A and 7B, the small molecule profile of the controls were compared to that of the subjects having Parkinson's disease. The subjects suffering from Parkinson's disease showed much more variation in the concentrations of many different metabolites.

Depression

For depression, plasma samples from healthy controls were compared to those of subjects suffering from depression. The subjects suffering from depression were divided into groups being treated with particular medications and an untreated groups. The groups were further compared with a group of subjects on remission.

In Figures 8A and 8B, the small molecule profile of the controls (8A) were compared to that of the depressed subjects (8B). The subjects suffering from depression show a much more variation in the concentrations of many different metabolites. Comparison of the treated groups show that treatment generally shifts the small molecule profiles to a more normal small molecule profile.

Figure 9 is a discriminate analysis plot which shows the differences between the control, depressed and subjects on remission.

Schizophrenia

For schizophrenia, plasma samples from healthy controls were compared to those of subjects suffering from schizophrenia. The groups were matched with respect to age and gender.

In Figure 10, the small molecule profile of the controls (blue) are compared to that of the subjects having schizophrenia (red). The subjects suffering from schizophrenia showed a much more variation in the concentrations of many different metabolites.

9. It is my opinion that the present specification enables one of ordinary skill in the art to practice the claimed invention. The data and examples presented in this declaration show that by using the methods described in the instant specification, an ordinarily skilled artisan, at the time the application was filed, could have used the

specification to practice the claimed invention. The ordinarily skilled artisan, in possession of the instant specification, would have been able to identify compounds indicative of a nervous system disorder by comparing a small molecule profile of a subject having the disorder to a standard small molecule profile, and thus been able to identify small molecules indicative of the nervous system disorder.

10. I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of Title XVIII of the United States Code, and that such willful false statements may jeopardize the validity of this Application for Patent or any patent issuing thereon.

John Ryals, Ph.D.

12/04/06
Date